The Mythology of Plasma Transfusion

Jonathan H. Waters, MD,*† and Mark H. Yazer, MD‡§

Men learn little from others' experience. But in the life of one man, never the same time returns.

-T. S. Eliot in Murder in the Cathedral (1935)

any myths exist regarding plasma transfusion. In this issue of Anesthesia & Analgesia, Warner et al¹ explore several of these myths. The authors found that patients with abnormal international normalized ratios (INRs) were typically administered 2 units of plasma and that this 2-unit transfusion had very little effect on the patient's INR. This might be a surprising finding to many. Most clinicians will order plasma in 2-unit doses expecting to see reversal of a patient's coagulopathy. So why did Warner et al¹ find no effect? Before revealing the reason, it is important to note that the effect of plasma transfusion on INR reversal was the focus of research in transfusion medicine over a decade ago, yet there seems to have been little knowledge transfer to the world of the anesthesiologist or surgeon. This lack of knowledge transfer is why the study of Warner et al¹ is so important for us in the operating room environment to understand. Plasma is the second most commonly transfused blood product.² In Warner's medical center, anesthesiologists were responsible for 63% of the plasma transfusions and 55% of these transfusions were for INRs <2.0. Understanding where plasma transfusion has benefit and where it does not is paramount in minimizing risks associated with plasma transfusion.

One of the primary observations of Warner et al¹ is that a very small decrease in INR occurs after a 2-unit plasma transfusion. In 2006, Holland and Brooks³ modeled the effect of plasma transfusion on the INR, which is demonstrated in the Figure. What is seen is that the higher the patient's starting INR, the greater the effect of plasma transfusion has in lowering it; whereas, at a low starting INR, the effect of plasma transfusion is minimal. Additionally, one can see that >2 units of plasma is required to correct a high INR into a more normal range and that, even after

From the *Department of Anesthesiology & Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania; †McGowan Institute for Regenerative Medicine, Pittsburgh, Pennsylvania; ‡The Institute for Transfusion Medicine, Pittsburgh, Pennsylvania; and §Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania.

Accepted for publication April 30, 2018.

Funding: None.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Jonathan H. Waters, MD, Department of Anesthesiology, Magee Women's Hospital of UPMC, 300 Halket St, Suite 3510, Pittsburgh, PA 15213. Address e-mail to watejh@upmc.edu.

Copyright © 2018 International Anesthesia Research Society DOI: 10.1213/ANE.00000000003505



Figure. This figure relates the amount of plasma that is necessary to correct an international normalized ratio (INR). What is important to note is that INR change is minimal at lower starting INRs, whereas at higher INRs, the impact is larger. It is also important to note that the INR never totally normalizes to 1.

transfusing multiple units of plasma, the INR achieved never really reaches 1.0. Why is this? Part of it relates to the INR of the plasma being transfused. The INR of plasma reflects the INR of the donor and typically ranges from 0.9 to 1.3.⁴ So if a patient with a minimal INR elevation of 1.2 is given a plasma unit with an INR of 1.2, nothing will happen to the patient other than having been exposed to the risks of transfusion-associated circulatory overload, transfusionrelated acute lung injury, and anaphylaxis.

Another issue affecting INR correction is that the relationship between coagulation factor concentration and INR is nonlinear. Normal hemostasis occurs when coagulation factor concentrations are generally >30%, which correlates with an INR of approximately 1.7.5 Transfusion of plasma to raise the patient's coagulation factor concentration by 10% from 30% to 40% will change a starting INR of 1.7 very little, perhaps down slightly to 1.6. However, when the patient's starting INR is 3.0 and coagulation factor concentrations are <10% of normal, a 10% rise in coagulation factor concentrations will drop the INR to approximately 2.1. Thus, at a higher starting INR, the effect of plasma is much greater than at a lower starting INR. This nonlinear relationship suggests that small elevations in the INR should not be corrected because they basically cannot be corrected with plasma, yet large elevations in the INR can indeed be corrected with plasma.

This raises another issue which is how much plasma is needed to raise coagulation factor concentrations by 10%. At the time of donation, the average donor has 1 IU/mL of all coagulation factors. Because the procoagulant content of the unit is diluted by anticoagulant, a 250-mL unit of plasma might be expected to provide approximately 200

August 2018 • Volume 127 • Number 2

Copyright © 2018 International Anesthesia Research Society. Unauthorized reproduction of this article is prohibited.

units of procoagulant activity, on average. Recovery of factors in plasma is not 100%; however, and may be as low as 20%–40%. Thus, in a 70-kg patient with a plasma volume of 3000 mL, transfusion of one 250 mL unit of plasma might be expected to increase most factors by about 2.5%. Transfusion of 4 units would raise the level by about 10%. This explains Warner et al's¹ finding that INR changes were modest when the starting INR was <3.0 and that patients were far more likely to achieve 50% normalization of the INR when >3 units of plasma were given.

Another finding of Warner et al's¹ report was that 20% of plasma was given prophylactically to stable, nonbleeding patients before a procedure to correct an abnormal INR. Remembering that normal hemostasis occurs when the coagulation factors are generally at least 30% activity and that this activity correlates to an INR of approximately 1.7, administration of plasma will have a minimal impact on reducing the INR. If one considers a preoperative surgical patient who has a minimally elevated INR, and this patient is transfused with plasma preoperatively and does not bleed during their procedure, it might reinforce the belief that the plasma transfusion was the reason why the patient did not bleed. The fallacy here is that a minimally abnormal INR predicts surgical bleeding risk. This lack of the INR's predictive ability has been demonstrated in numerous studies and was the focus of a systematic review which showed no relationship between abnormal INR values and procedural bleeding.6

If investigation into the effects of plasma transfusion was performed in the blood banking community a decade ago, it raises the question as to why this knowledge has not been transferred to the clinical world. We would suggest that part of the reason arises from a lack of transfusion education. The lack of education starts as medical students where the exposure to transfusion medicine topics is limited. In 17% of medical schools, there is no formal exposure to transfusion medicine. For 50% of American medical schools, only 1–2 hours of training is provided.⁷ One to 2 hours is barely enough time to learn the ABO blood groups and to know what crossmatching means. There is a lack of data as to how much transfusion medicine education exists in a typical anesthesiology residency; however, there are some data on how knowledgeable anesthesiologists are about transfusion topics. In the United Kingdom, an objective structured clinical examination on transfusion was administered to a group of anesthesiologists where the pass rate was 58%.8 Whether this knowledge level is similar in the United States is currently being investigated.

Blood transfusion is the most common procedure performed on a hospitalized patient, occurring in 7.1% of all inpatient admissions and in over 10% of all patients over the age of 65 years old.⁹ The Joint Commission, the American Medical Association, the American Hospital Association, and the American Board of Internal Medicine with their Choosing Wisely Campaign have all identified blood transfusion as 1 of the 5 most overused medical therapies.¹⁰ Given how commonly transfusions are administered, it seems that transfusion medicine should be a core part of medical education, so that experience gained in the past can be learned afresh by new trainees. In our institution, we have created a 1-month rotation in transfusion medicine during an anesthesiology resident's PGY-1 year. We would encourage similar developments at institutions elsewhere.

DISCLOSURES

Name: Jonathan H. Waters, MD. Contribution: This author helped write and edit the manuscript. Name: Mark H. Yazer, MD. Contribution: This author helped write and edit the manuscript. This manuscript was handled by: Roman M. Sniecinski, MD.

REFERENCES

- Warner MA, Hanson AC, Weister TJ, et al. Changes in international normalized ratios after plasma transfusion of varying doses in unique clinical environments. *Anesth Analg.* 2018;127:349–357.
- Ellingson KD, Sapiano MRP, Haass KA, et al. Continued decline in blood collection and transfusion in the United States-2015. *Transfusion*. 2017;57(suppl 2):1588–1598.
- 3. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: The effect of plasma transfusion on coagulation test results. *Am J Clin Pathol.* 2006;126:133–139.
- Holland LL, Foster TM, Marlar RA, Brooks JP. Fresh frozen plasma is ineffective for correcting minimally elevated international normalized ratios. *Transfusion*. 2005;45:1234–1235.
- 5. Dzik WH. Component therapy before bedside procedures. In: Mintz PD, ed. *Transfusion Therapy: Clinical Principles and Practice*, 2nd ed. Bethesda, MD: American Association of Blood Banks Press; 2005: 1–26.
- Segal JB, Dzik WH; Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion*. 2005;45:1413–1425.
- O'Brien KL, Champeaux AL, Sundell ZE, Short MW, Roth BJ. Transfusion medicine knowledge in postgraduate year 1 residents. *Transfusion*. 2010;50:1649–1653.
- Corrie K, Wiles M, Flack J, Lamb J. A novel objective structured clinical examination for the assessment of transfusion practice in anaesthesia. *Clin Teach.* 2011;8:97–100.
- Statistical Brief #215. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; November 2016. Available at: www.hcup-us.ahrq. gov/reports/statbriefs/sb215-Red-Blood-Cell-Transfusions-Trends.jsp. Accessed March 9, 2018.
- Bulger J, Nickel W, Messler J, et al. Choosing wisely in hospital medicine. J Hosp Med. 2013;9:486–492. Proceedings from the National Summit on Overuse. September 24, 2012. Available at: https://www.jointcommission.org/assets/1/6/National_ Summit_Overuse.pdf. Accessed March 9, 2018.